CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074568

Trade Name : CIMETIDINE TABLETS 200, 300MG AND 400MG USP

Generic Name: Cimetidine Tablets 200mg, 300mg and 400mg USP

Sponsor : Sidmak Laboratories, Inc.

Approval Date: February 27, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074568

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074568

APPROVAL LETTER

ANDA 74-568

FEB 27 '97

Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. Box 371
East Hanover, NJ 07936

Dear Sir:

This is in reference to your abbreviated new drug application dated November 14, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cimetidine Tablets USP, 200 mg, 300 mg and 400 mg.

Reference is also made to your amendments dated April 6, 1995 and September 25, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cimetidine Tablets USP, 200 mg, 300 mg and 400 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Tagamet® Tablets, 200 mg, 300 mg and 400 mg of SmithKline Beecham Pharmaceuticals. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

2/27/97

Douglas L. Spörn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074568

FINAL PRINTED LABELING

Musculoskeletal: There have been rare reports of reversible arthralgia and myalgia; exacerbation of joint symptoms in patients with preexisting arthritis has also been reported. Such symptoms have usually been alleviated by a reduction in cimetidine dosage. Rare cases of polymyositis have been reported, but no causal relationship has been established.

Integumental: Mild rash and, very rarely, cases of severe generalized skin reactions including Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis and generalized exfoliative erythroderma have been reported with H_2-receptor antagonists. Reversible alopecia has been reported very rarely.

Immune Function: There have been extremely rare reports of strongyloidiasis hyperinfection in immunocompromised patients.

OVERDOSAGE: Studies in animals indicate that toxic doses are associated with respiratory failure and tachycardia which may be controlled by assisted respiration and the administration of a beta-blocker.

Reported acute ingestions orally of up to 20 g have been associated with transient adverse effects similar to those encountered in normal clinical experience. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

There have been reports of severe CNS symptoms, including unresponsiveness, following ingestion of between 20 and 40 grams of cimetidine, and extremely rare reports following concomitant use of multiple CNS-active medications and ingestion of cimetidine at doses less than 20 grams. An elderly, terminally ill dehydrated patient with organic brain syndrome receiving concomitant antipsychotic agents and cimetidine 4800 mg intravenously over a 24 hour period experienced mental deterioration with reversal on cimetidine discontinuation.

There have been two deaths in adults who have been reported to have ingested over 40 g orally on a single occasion.

DOSAGE AND ADMINISTRATION: Duodenal Ulcer:

Active Duodenal Ulcer: Clinical studies have indicated that suppression of nocturnal acid is the most important factor in duodenal ulcer healing (see **CLINICAL PHARMACOLOGY: Antisecretory Activity, Acid Secretion**). This is supported by recent clinical trials (see **CLINICAL PHARMACOLOGY: Clinical Trials: *Active Duodenal Ulcer***). Therefore, there is no apparent rationale, except for familiarity with use, for treating with anything other than a once-daily at bedtime oral dosage regimen (h.s.).

In a U.S. oral dose-ranging study of 400 mg h.s., 800 mg h.s. and 1600 mg h.s., a continuous dose response relationship for ulcer healing was demonstrated.

However, 800 mg h.s. is the dose of choice for most patients, as it provides a high healing rate (the difference between 800 mg h.s. and 1600 mg h.s. being small), maximal pain relief, a decreased potential for drug interactions (see **PRECAUTIONS: Drug Interactions**) and maximal patient convenience. Patients unhealed at four weeks, or those with persistent symptoms, have been shown to benefit from two to four weeks of continued therapy.

It has been shown that patients who both have an endoscopically demonstrated ulcer larger than 1 cm and are also heavy smokers (i.e., smoke one pack of cigarettes or more per day) are more difficult to heal. There is some evidence which suggests that more rapid healing can be achieved in this subpopulation with cimetidine 1600 mg at bedtime. While early pain relief with either 800 mg h.s. or 1600 mg h.s. is equivalent in all patients, 1600 mg h.s. provides an appropriate alternative when it is important to ensure healing within four weeks for this subpopulation. Alternatively, approximately 94% of all patients will also heal in eight weeks with cimetidine 800 mg h.s.

Other cimetidine oral regimens in the U.S. which have been shown to be effective are: 300 mg four times daily, with meals and at bedtime, the original regimen with which U.S. physicians have the most experience, and 400 mg twice daily, in the morning and at bedtime (see **CLINICAL PHARMACOLOGY: Clinical Trials: *Active Duodenal Ulcer***).

Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of cimetidine.

While healing with cimetidine often occurs during the first week or two, treatment should be continued for 4 to 6 weeks unless healing has been demonstrated by endoscopic examination.

Maintenance Therapy for Duodenal Ulcer: In those patients requiring maintenance therapy, the recommended adult oral dose is 400 mg at bedtime.

Active Benign Gastric Ulcer: The recommended adult oral dosage for short-term treatment of active benign gastric ulcer is 800 mg h.s., or 300 mg four times a day with meals and at bedtime. Controlled clinical studies were limited to six weeks of treatment (see **CLINICAL PHARMACOLOGY: Clinical Trials**). 800 mg h.s. is the preferred regimen for most patients based upon convenience and reduced potential for drug interactions. Symptomatic response to cimetidine does not preclude the presence of a gastric malignancy. It is important to follow gastric ulcer patients to assure rapid progress to complete healing.

Erosive Gastroesophageal Reflux Disease (GERD): The recommended adult oral dosage for the treatment of erosive esophagitis that has been diagnosed by endoscopy is 1600 mg daily in divided doses (800 mg b.i.d. or 400 mg q.i.d.) for 12 weeks. The use of cimetidine beyond 12 weeks has not been established.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome): Recommended adult oral dosage: 300 mg four times a day with meals and at bedtime. In some patients it may be necessary to administer higher doses more frequently. Doses should be adjusted to individual patient needs, but should not usually exceed 2400 mg per day and should continue as long as clinically indicated.

Dosage Adjustment for Patients with Impaired Renal Function: Patients with severely impaired renal function have been treated with cimetidine. However, such usage has been very limited. On the basis of this experience, the recommended dosage is 300 mg every 12 hours orally or by intravenous injection. Should the patient's condition require, the frequency of dosing may be increased to every 8 hours or even further with caution. In severe renal failure, accumulation may occur and the lowest frequency of dosing compatible with an adequate patient response should be used. When liver impairment is also present, further reductions in dosage may be necessary. Hemodialysis reduces the level of circulating cimetidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: Cimetidine Tablets, USP:

200 mg- Light yellow, round, unscored, film coated tablets in bottles of 100, 250, 500, and 1000.
Printed: SL 549

300 mg- Light yellow, round, unscored, film coated tablets in bottles of 100, 250, 500, and 1000.
Printed: SL 550

400 mg- Light yellow, capsule shaped, scored, film coated tablets in bottles of 60, 100, 250, 500, and 1000.
Printed: SL 551

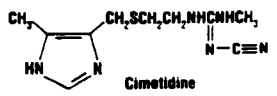
800 mg- Light yellow, capsule shaped, scored, film coated tablets in bottles of 30, 100 and 500.
Printed: SL 552

Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a tight, light-resistant container as defined in the USP.
CAUTION: Federal law prohibits dispensing without prescription.

Manufactured by
SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

Description: Cimetidine is a histamine H_2-receptor antagonist. Chemically it is *N*"-cyano-*N*-methyl-*N*'-[2-[[5-methyl-1*H*-imidazol-4-yl)methyl]thio]-ethyl guanidine.

The molecular formula for cimetidine is $C_{10}H_{16}N_6S$, this represents a molecular weight of 252.34. The structural formula of cimetidine is



Cimetidine

Cimetidine contains an imidazole ring, and is chemically related to histamine.

Cimetidine has a bitter taste and characteristic odor.

Solubility Characteristics: Cimetidine is soluble in alcohol, slightly soluble in water, very slightly soluble in chloroform and insoluble in ether.

P08-0549

CIMETIDINE TABLETS, USP

Iss. 6/96

Each tablet, for oral administration, contains 200 mg, 300 mg, 400 mg or 800 mg of cimetidine. In addition, each tablet contains the following inactive ingredients: artificial flavor, carnauba wax, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, polysorbate 80, sodium lauryl sulfate, titanium dioxide, D&C Yellow #10, FD&C Yellow #6, and synthetic black iron oxide. The 200 mg, 300 mg and 400 mg tablets also contain colloidal silicon dioxide, pregelatinized starch and sodium starch glycolate. The 800 mg tablets also contain crospovidone and silicon dioxide.

CLINICAL PHARMACOLOGY: Cimetidine competitively inhibits the action of histamine at the histamine H_2 receptors of the parietal cells and thus is a histamine H_2-receptor antagonist.

Cimetidine is not an anticholinergic agent. Studies have shown that cimetidine inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin.

Antisecretory Activity:

1) Acid Secretion: *Nocturnal:* Cimetidine 800 mg orally at bedtime reduces mean hourly H^+ activity by greater than 85% over an eight-hour period in duodenal ulcer patients, with no effect on daytime acid secretion. Cimetidine 1600 mg orally h.s. produces 100% inhibition of mean hourly H^+ activity over an eight-hour period in duodenal ulcer patients, but also reduces H^+ activity by 35% for an additional five hours into the following morning. Cimetidine 400 mg b.i.d. and 300 mg q.i.d. decrease nocturnal acid secretion in a dose-related manner, i.e., 47% to 83% over a six- to eight-hour period and 54% over a nine-hour period, respectively.

Food Stimulated: During the first hour after a standard experimental meal, oral cimetidine 300 mg inhibited gastric acid secretion in duodenal ulcer patients by at least 50%. During the subsequent two hours cimetidine inhibited gastric acid secretion by at least 75%.

The effect of a 300 mg breakfast dose of cimetidine continued for at least four hours and there was partial suppression of the rise in gastric acid secretion following the luncheon meal in duodenal ulcer patients. This suppression of gastric acid output was enhanced and could be maintained by another 300 mg dose of cimetidine given with lunch.

In another study, cimetidine 300 mg given with the meal increased gastric pH as compared with placebo.

Mean Gastric pH

	Cimetidine	Placebo
1 hour	3.5	2.6
2 hours	3.1	1.6
3 hours	3.8	1.9
4 hours	6.1	2.2

24-hour Mean H^+ Activity: Cimetidine 800 mg h.s., 400 mg b.i.d. and 300 mg q.i.d. all provide a similar, moderate (less than 60%) level of 24-hour acid suppression. However, the 800 mg h.s. regimen exerts its entire effect on nocturnal acid, and does not affect daytime gastric physiology.

Chemically Stimulated: Oral cimetidine significantly inhibited gastric acid secretion stimulated by betazole (an isomer of histamine), pentagastrin, caffeine and insulin as follows:

Stimulant	Stimulant Dose		Cimetidine		% Inhibition
Betazole	1.5 mg/kg	(sc)	300 mg	(po)	85% at 2 1/2 hours
Pentagastrin	6 mcg/kg/hr	(iv)	100 mg/hr	(iv)	60% at 1 hour
Caffeine	5 mg/kg/hr	(iv)	300 mg	(po)	100% at 1 hour
Insulin	0.03 units/kg/hr	(iv)	100 mg/hr	(iv)	82% at 1 hour

When food and betazole were used to stimulate secretion, inhibition of hydrogen ion concentration usually ranged from 45% to 75% and the inhibition of volume ranged from 30% to 65%.

2) Pepsin: Oral cimetidine 300 mg reduced total pepsin output as a result of the decrease in volume of gastric juice.

3) Intrinsic Factor: Intrinsic factor secretion was studied with betazole as a stimulant. Oral cimetidine 300 mg inhibited the rise in intrinsic factor concentration produced by betazole, but some intrinsic factor was secreted at all times.

Other: Lower Esophageal Sphincter Pressure and Gastric Emptying:

Cimetidine has no effect on lower esophageal sphincter (LES) pressure or the rate of gastric emptying.

Pharmacokinetics: Cimetidine is rapidly absorbed after oral administration and peak levels occur in 45 to 90 minutes. The half-life of cimetidine is approximately 2 hours. Both oral and parental (IV or IM) administration provide comparable periods of therapeutically effective blood levels; blood concentrations remain above that required to provide 80% inhibition of basal gastric acid secretion for 4 to 5 hours following a dose of 300 mg.

The principal route of excretion of cimetidine is the urine. Following parenteral administration, most of the drug is excreted as the parent compound; following oral administration, the drug is more extensively metabolized, the sulfoxide being the major metabolite. Following a single oral dose, 48% of the drug is recovered from the urine after 24 hours as the parent compound. Following IV or IM administration, approximately 75% of the drug is recovered from the urine after 24 hours as the parent compound.

Clinical Trials: Duodenal Ulcer: Cimetidine has been shown to be effective in the treatment of active duodenal ulcer and, at reduced dosage, in maintenance therapy following healing of active ulcers.

Active Duodenal Ulcer: Cimetidine accelerates the rate of duodenal ulcer healing. Healing rates reported in U.S. and foreign controlled trials with oral cimetidine are summarized below, beginning with the regimen providing the lowest nocturnal dose.

Duodenal Ulcer Healing Rates with Various Cimetidine Dosage Regimens*

Regimen	300 mg q.i.d.	400 mg b.i.d.	800 mg h.s.	1600 mg h.s.
week 4	68%	73%	80%	86%
week 6	80%	80%	89%	----
week 8	----	92%	94%	----

* Averages from controlled clinical trials

A U.S., double-blind, placebo-controlled, dose-ranging study demonstrated that all once-daily at bedtime (h.s.) cimetidine regimens were superior to placebo in ulcer healing and that cimetidine 800 mg h.s. healed 75% of patients at four weeks. The healing rate with 800 mg h.s. was significantly superior to 400 mg h.s. (66%) and not significantly different from 1600 mg h.s. (81%).

In the U.S. dose-ranging trial, over 80% of patients receiving cimetidine 800 mg h.s. experienced nocturnal pain relief after one day. Relief from daytime pain was reported in approximately 70% of patients after two days. As with ulcer healing, the 800 mg h.s. dose was superior to 400 mg h.s. and not different from 1600 mg h.s.

In foreign, double-blind studies with cimetidine 800 mg h.s., 79% to 85% of patients were healed at four weeks.

While short-term treatment with cimetidine can result in complete healing of the duodenal ulcer, acute therapy will not prevent ulcer recurrence after cimetidine has been discontinued. Some follow-up studies have reported that the rate of recurrence once therapy was discontinued was slightly higher for patients healed on cimetidine than for patients healed on other forms of therapy; however, the cimetidine-treated patients generally had more severe disease.

Maintenance Therapy in Duodenal Ulcer: Treatment with a reduced dose of cimetidine has been proven effective as maintenance therapy following healing of active duodenal ulcers.

In numerous placebo-controlled studies conducted worldwide, the percent of patients with observed ulcers at the end of one year's therapy with cimetidine 400 mg h.s. was significantly lower (10% to 45%) than in patients receiving placebo (44% to 70%). Thus, from 55% to 90% of patients were maintained free of observed ulcers at the end of one year with cimetidine 400 mg h.s.

Factors such as smoking, duration and severity of disease, gender, and genetic traits may contribute to variations in actual percentages.

Trials of other anti-ulcer therapy, whether placebo-controlled, positive-controlled or open, have demonstrated a range of results similar to that seen with cimetidine.

Active Benign Gastric Ulcer: Cimetidine has been shown to be effective in the short-term treatment of active benign gastric ulcer.

In a multicenter, double-blind U.S. study, patients with endoscopically **confirmed benign gastric** ulcer were treated with cimetidine 300 mg four times a day or with placebo for six weeks. Patients were limited to those with ulcers ranging from 0.5 to 2.5 cm in size. Endoscopically confirmed healing at six weeks was seen in significantly* more cimetidine-treated patients than in patients receiving placebo, as shown below:

	Cimetidine	Placebo
week 2	14/63 (22%)	7/63 (11%)
total at week 6	43/65 (66%)*	30/67 (45%)

*p<0.05

In a similar multicenter U.S. study of the 800 mg h.s. oral regimen, the endoscopically confirmed healing rates were:

	Cimetidine	Placebo
total at week 6	63/83 (76%)*	44/80 (55%)

*p=0.005

Similarly, in worldwide double-blind clinical studies, endoscopically evaluated benign gastric ulcer healing rates were consistently higher with cimetidine than with placebo.

Gastroesophageal Reflux Disease (GERD): In two multicenter, double-blind, placebo-controlled studies in patients with gastroesophageal reflux disease (GERD) and endoscopically proven erosions and/or ulcers, cimetidine was significantly more effective than placebo in healing lesions. The endoscopically confirmed healing rates were:

Trial		Cimetidine (800 mg b.i.d.)	Cimetidine (400 mg q.i.d.)	Placebo	p-Value (800 mg b.i.d. vs. placebo)
1	week 6	45%	52%	26%	0.02
	week 12	60%	66%	42%	0.02
2	week 6	50%		20%	<0.01
	week 12	67%		36%	<0.01

In these trials cimetidine was superior to placebo by most measures in improving symptoms of day- and night-time heartburn, with many of the differences statistically significant. The q.i.d. regimen was generally somewhat better than the b.i.d. regimen where these were compared.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison Syndrome): Cimetidine significantly inhibited gastric acid secretion and reduced occurrence of diarrhea, anorexia and pain in patients with pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas. Use of cimetidine was also followed by healing of intractable ulcers.

INDICATIONS AND USAGE: Cimetidine tablets are indicated in:

(1) **Short-term treatment of active duodenal ulcer.** Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks (see **DOSAGE AND ADMINISTRATION: Duodenal Ulcer**). Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended since antacids have been reported to interfere with the absorption of oral cimetidine.

(2) **Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer.** Patients have been maintained on continued treatment with cimetidine 400 mg h.s. for periods of up to five years.

(3) **Short-term treatment of active benign gastric ulcer.** There is no information concerning usefulness of treatment periods of longer than 8 weeks.

(4) **Erosive gastroesophageal reflux disease (GERD).** Erosive esophagitis diagnosed by endoscopy. Treatment is indicated for 12 weeks for healing of lesions and control of symptoms. The use of cimetidine beyond 12 weeks has not been established (see **DOSAGE AND ADMINISTRATION: GERD**).

(5) **The treatment of pathological hypersecretory conditions** (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).

CONTRAINDICATIONS: Cimetidine tablets are contraindicated for patients to have hypersensitivity to the product.

PRECAUTIONS: General: Symptomatic response to cimetidine therapy does not preclude the presence of a gastric malignancy. There have been rare reports of transient healing of gastric ulcers despite subsequently documented malignancy.

Reversible confusional states (see **ADVERSE REACTIONS**) have been observed on occasion, predominantly, but not exclusively, in severely ill patients. Advancing age (50 or more years) and preexisting liver and/or renal disease appear to be contributing factors. In some patients these confusional states have been mild and have not required discontinuation of cimetidine therapy. In cases where discontinuation was judged necessary, the condition usually cleared within 3 to 4 days of drug withdrawal.

Drug Interactions: Cimetidine, apparently through an effect on certain microsomal enzyme systems, has been reported to reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, nifedipine, chlordiazepoxide, diazepam, certain tricyclic antidepressants, lidocaine, theophylline and metronidazole, thereby delaying elimination and increasing blood levels of these drugs.

Clinically significant effects have been reported with the warfarin anticoagulants; therefore, close monitoring of prothrombin time is recommended, and adjustment of the anticoagulant dose may be necessary when cimetidine is administered concomitantly. Interaction with phenytoin, lidocaine and theophylline has also been reported to produce adverse clinical effects.

However, a crossover study in healthy subjects receiving either cimetidine 300 mg q.i.d. or 800 mg h.s. concomitantly with a 300 mg b.i.d. dosage of theophylline extended-release tablets demonstrated less alteration in steady-state theophylline peak serum levels with the 800 mg h.s. regimen, particularly in subjects aged 54 years and older. Data beyond ten days are not available. (Note: All patients receiving theophylline should be monitored appropriately, regardless of concomitant drug therapy.)

Dosage of the drugs mentioned above and other similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered cimetidine to maintain optimum therapeutic blood levels.

Alteration of pH may affect absorption of certain drugs (e.g., ketoconazole). If these products are needed, they should be given at least 2 hours before cimetidine administration.

Additional clinical experience may reveal other drugs affected by the concomitant administration of cimetidine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 24-month toxicity study conducted in rats, at dose levels of 150, 378 and 950 mg/kg/day (approximately 8 to 48 times the recommended human dose), there was a small increase in the incidence of benign Leydig cell tumors in each dose group; when the combined drug-tested groups and control groups were compared, this increase reached statistical significance. In a subsequent 24-month study, there were no differences between the rats receiving 150 mg/kg/day and the untreated controls. However, a statistically significant increase in benign Leydig cell tumor incidence was seen in the rats that received 378 and 950 mg/kg/day. These tumors were common in control groups as well as treated groups and the difference became apparent only in aged rats.

Cimetidine has demonstrated a weak antiandrogenic effect, in animal studies this was manifested as reduced prostate and seminal vesicle weights. However, there was no impairment of mating performance or fertility, nor any harm to the fetus in these animals at doses 8 to 48 times the full therapeutic dose of cimetidine, as compared with controls. The cases of gynecomastia seen in patients treated for one month or longer may be related to this effect.

In human studies, cimetidine has been shown to have no effect on spermatogenesis, sperm count, motility, morphology, or *in vitro* fertilizing capacity.

Pregnancy: Teratogenic Effects. Pregnancy Category B. Reproduction studies have been performed in rats, rabbits and mice at doses up to 40 times the normal human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cimetidine.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Cimetidine is secreted in human milk and, as a general rule, nursing should not be undertaken while a patient is on a drug.

Pediatric Use: Clinical experience in pediatric patients is limited. Therefore, cimetidine therapy cannot be recommended for pediatric patients under 16, unless, in the judgment of the physician, anticipated benefits outweigh the potential risks. In very limited experience, doses of 20 to 40 mg/kg per day have been used.

Immunocompromised Patients: In immunocomprised patients, decreased gastric acidity, including that produced by acid-suppressing agents such as cimetidine, may increase the possibility of a hyperinfection of strongyloidiasis.

ADVERSE REACTIONS: Adverse effects reported in patients taking cimetidine are described below by body system. Incidence figures of 1 in 100 and greater are generally derived from controlled clinical studies.

Gastrointestinal: Diarrhea (usually mild) has been reported in approximately 1 in 100 patients.

CNS: Headaches ranging from mild to severe, have been reported in 3.5% of 924 patients taking 1600 mg/day, 2.1% of 2,225 patients taking 800 mg/day and 2.3% of 1,897 patients taking placebo. Dizziness and somnolence (usually mild) have been reported in approximately 1 in 100 patients on either 1600 mg/day or 800 mg/day.

Reversible confusional states, e.g., mental confusion, agitation, psychosis, depression, anxiety, hallucinations, disorientation, have been reported predominantly, but not exclusively, in severely ill patients. They have usually developed within 2 to 3 days of initiation of cimetidine therapy and have cleared within 3 to 4 days of discontinuation of the drug.

Endocrine: Gynecomastia has been reported in patients treated for one month or longer. In patients being treated for pathological hypersecretory states, this occurred in about 4% of cases while in all others the incidence was 0.3% to 1% in various studies. No evidence of induced endocrine dysfunction was found, and the condition remained unchanged or returned toward normal with continuing cimetidine treatment.

Reversible impotence has been reported in patients with pathological hypersecretory disorders, e.g., Zollinger-Ellison Syndrome, receiving cimetidine, particularly in high doses, for at least 12 months (range 12 to 79 months, mean 38 months). However, in large-scale surveillance studies at regular dosage, the incidence has not exceeded that commonly reported in the general population.

Hematologic: Decreased white blood cell counts in cimetidine-treated patients (approximately 1 per 100,000 patients), including agranulocytosis (approximately 3 per million patients), have been reported, including a few reports of recurrence on rechallenge. Most of these reports were in patients who had serious concomitant illnesses and received drugs and/or treatment known to produce neutropenia. Thrombocytopenia (approximately 3 per million patients) and, very rarely, cases of pancytopenia or aplastic anemia have also been reported. As with some other H_2-receptor antagonists, there have been extremely rare reports of immune hemolytic anemia.

Hepatobiliary: Dose-related increases in serum transaminase have been reported. In most cases they did not progress with continued therapy and returned to normal at the end of therapy. There have been rare reports of cholestatic or mixed cholestatic-hepatocellular effects. These were usually reversible. Because of the predominance of cholestatic features, severe parenchymal injury is considered highly unlikely. However, as in the occasional liver injury with other H_2-receptor antagonists, in exceedingly rare circumstances fatal outcomes have been reported.

There has been reported a single case of biopsy-proven periportal hepatic fibrosis in a patient receiving cimetidine.

Rare cases of pancreatitis, which cleared on withdrawal of the drug, have been reported.

Hypersensitivity: Rare cases of fever and allergic reactions including anaphylaxis and hypersensitivity vasculitis, which cleared on withdrawal of the drug, have been reported.

Renal: Small, possibly dose-related increases in plasma creatinine, presumably due to competition for renal tubular secretion, are not uncommon and do not signify deteriorating renal function. Rare cases of interstitial nephritis and urinary retention, which cleared on withdrawal of the drug, have been reported.

Cardiovascular: Rare cases of bradycardia, tachycardia and A-V heart block have been reported with H_2-receptor antagonists.

P08-0549

NDC 50111-551-04

Cimetidine Tablets, USP

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

60 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 11/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APPROVED FEB 27 1997

N 3 50111-551-04 6

NDC 50111-551-01

Cimetidine Tablets, USP

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 11/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APPROVED FEB 27 1997

N 3 50111-551-01 5

NDC 50111-551-06

Cimetidine Tablets, USP

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 11/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APPROVED FEB 27 1997

N 3 50111-551-06 0

NDC 50111-551-02

Cimetidine Tablets, USP

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.

N 3 50111-551-02 2

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APPROVED FEB 27 1997

Control No.:
Exp. Date:
Iss. 11/95

NDC 50111-551-03

Cimetidine Tablets, USP

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 400 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.

N 3 50111-551-03 9

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APPROVED FEB 27 1997

Control No.:
Exp. Date:
Iss. 11/95

NDC 50111-549-01

Cimetidine Tablets, USP

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 200 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 11/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-549-01 2

APPROVED FEB 27 1997

NDC 50111-549-06

Cimetidine Tablets, USP

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

250 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 200 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 11/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-549-06 7

APPROVED FEB 27 1997

NDC 50111-549-02

Cimetidine Tablets, USP

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 200 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.
Control No.:
Exp. Date:
Iss. 11/95

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

N 3 50111-549-02 9

APPROVED FEB 27 1997

NDC 50111-549-03

Cimetidine Tablets, USP

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Sidmak LABORATORIES, INC.

EACH TABLET CONTAINS:
Cimetidine, USP ..... 200 mg
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
USUAL DOSAGE: See package insert.

N 3 50111-549-03 6

SIDMAK LABORATORIES, INC.
East Hanover, NJ 07936

APPROVED FEB 27 1997

Control No.:
Exp. Date:
Iss. 11/95

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074568

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-568

3. NAME AND ADDRESS OF APPLICANT
Sidmak Laboratories, Inc.
Attention: Arun D. Kulkarni
17 West Street
P.O. Box 371
East Hanover, NJ 07936

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Cimetidine, USP

9. AMENDMENTS AND OTHER DATES:

Firm		FDA
Orig. Submission	11/14/94	Ack. Letter 12/6/94
NA Letter	3/31/95	
Amendment	11/22/95	
NA Letter	4/25/96	
Amendment	9/25/96	

10. PHARMACOLOGICAL CATEGORY
Anti-Ulcer

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Tablet

14. POTENCY
200 mg
300 mg
400 mg

15. CHEMICAL NAME AND STRUCTURE
N''-Cyano-N-methyl-N'-[2-[[(5-methyl-1H-imidazol-4-yl)methyl]thio]-ethyl]- (USP drug substance)
(USP drug product)

17. COMMENTS
See text of review.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable.

19. REVIEWER:
Andrew J. Langowski

DATE COMPLETED:
1/2/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074568

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/~~AADA~~ # 74-568 SPONSOR: Sidmak Labs
DRUG: Cimetidine
DOSAGE FORM: Tablets
STRENGTH(s): 200, 300, & 400 mg
TYPE OF STUDY: (Single)/Multiple (Fasting)/Fed
STUDY SITE:

STUDY SUMMARY: The data of 24 out of the 26 subjects who completed the fasting study resulted in the 90% confidence interval of (0.89; 1.01), (0.92; 1.01) and (0.92; 1.13) for $LNAUC_{0-t}$, $LNAUC_{0-inf}$ and LNC_{max} respectively. The data of 24 out of the 26 subjects who completed the non-fasting study resulted in the ratios of the means of 1.01, 1.02 and 1.01 for AUC_{0-t}, AUC_{0-inf} and C_{max} respectively, when compare both formulations under non-fasting condition. Co-administration with food essentially did not affect the rate and extent of absorption.

DISSOLUTION: The tests were conducted in 900 mL of water, using USP XXII basket apparatus at 100 rpm. The results are acceptable according to the specification of "not less than of cimetidine in the dosage form is dissolved in 15 minutes" as published USP23.

PRIMARY REVIEWER: BRANCH:

INITIAL: DATE: 6/16/95

BRANCH CHIEF: BRANCH:

INITIAL: DATE: 6/16/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DATE: 6/16/95

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE: 6/28/95

JUN 15 1995

Cimetidine
Tablets, 200, 300 & 400 mg
ANDA # 74-568
Reviewer: L. Chuang

Sidmak Laboratories, Inc.
East Hanover, New Jersey
Submission Date:
November 14, 1994
April 6, 1995

Review of In-Vivo Bioequivalence Studies, Dissolution Data and Waiver Request

Introduction:

Cimetidine is a histamine H_2-receptor antagonist which inhibits both daytime and nocturnal basal gastric acid secretion. Cimetidine also inhibits gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin. It is indicated in the short-term treatment of active duodenal ulcer, and promotes healing in most patients within 4 weeks.

Following intravenous administration, the plasma concentration profile follows multicompartmental characteristics. The total systemic clearance is high (500 to 600 mL/min) and is mainly determined by renal clearance. The volume of distribution is about 1 L/kg. Elimination half-life is approximately 2 hours. Following oral administration of cimetidine, 2 plasma concentration peaks are frequently observed at about 1 hour and 3 hours, probably due to discontinuous absorption in the intestine or individual variation in gastric emptying (but not enteronepatic recycling since the biliary excretion rate in man is less than 2%). The absolute bioavailability is about 60% in healthy subjects and around 70% in peptic ulcer patients. Absorption and clearance of cimetidine are linear following 200 and 800 mg doses. When given with food, the extent of absorption of the drug remains unchanged but the time to reach the maximum peak concentration is delayed with only one peak in the plasma concentration curve observed at about 2 hours. Plasma protein binding of cimetidine is 20% and does not significantly affect the pharmacokinetics of the drug. Cimetidine distributes extensively into kidney, lung and muscle tissues, but less than 1% into the cerebrospinal fluid.

Cimetidine is available commercially as Tagamet® oral, film-coated tablets, 200, 300, 400 and 800 mg, manufactured by SmithKline Beecham. For treatment of active duodenal ulcer, the usual adult oral dosage of cimetidine is 800 mg daily at bedtime. For maintenance therapy following healing of acute duodenal ulcer, the usual oral dosage of cimetidine is 400 mg daily at bedtime. For the treatment of pathologic hypersecretory

conditions, the usual adult oral dosage is 300 mg 4 times daily with meals and at bedtime. For the treatment of active benign gastric ulcer, the usual adult oral dosage is 800 mg at bedtime or 300 mg 4 times daily with meals and at bedtime.

Bioequivalence Study - 400 mg strength -Fasting:

The objective of this study is to compare the bioavailability of Cimetidine 400 mg tablets, manufactured by Sidmak Laboratories, and Tagamet® 400 mg tablets, manufactured by SmithKline & Beecham under fasting condition.

The clinical portion of the study was conducted at

during March 9-11 and 23-25, 1992 with as the director of the clinical research. The analytical portion was performed in the during April 2-24, 1992 with as the analyst.

The design was a single-dose, 2-way crossover in fasting male volunteers. The protocol submitted by the firm was dated March 4, 1992. However the protocol that was approved by the Institutional Review Board was dated January 23, 1992 and approved February 18, 1992.

Upon request from the Agency, the firm submitted explanation for the discrepancy in the dates stated above (see submission of April 6, 1995). The firm stated that the protocol was originally prepared on January 23, 1992. When reviewed by the IRB on February 18, 1992, minor changes were made, i.e., addition of two blood sampling time points (hour 10 and hour 15) and inclusion of differential leukocyte in the laboratory test, and resulted in the protocol dated March 4, 1992.

According to the protocol of March 4, 1992, 26 Caucasian male volunteers were enrolled. They were 19-43 years old, weighed within ±15% of the ideal weight for their height and frame size, and 16 were regular users of tobacco products. The screening procedures included obtaining records of medical history and demographic data and laboratory tests of hemotology, serum chemistry, urinalysis and HIV test. The protocol stated that only medically healthy subjects with clinically normal laboratory profiles would be enrolled in the study. However, 21 of the 26 subjects enrolled had abnormal results of hematology and/or urinalysis. These abnormal results were considered not

clinically significant by the investigator.

Exclusion criteria were history or presence of any significant diseases, presence of idiosyncratic reaction to cimetidine, alcoholism or drug abuse within the last year, abnormal diet during 4 weeks preceding the study, donation of more than 500 mL of blood in 14 days, 750 mL in 3 months, 100 mL in 6 months, 1500 mL in 9 months or 2000 mL in a year, and completion of another clinical trial within 28 days of study start.

All 26 qualified volunteers were instructed not to take any medication for 7 days preceding the study, not to consume alcohol- or xanthine-containing beverage and foods for 24 hours before dosing and throughout the period of blood sample collection, and sign the informed consent form. After a supervised overnight fast, every subjects received one of the following randomly assigned drug treatments :

Treatment A - Test Drug: Cimetidine tablet, 1 x 400 mg, Sidmak Laboratories Inc., lot #92-008T, potency 98.1% and lot size of tablets.

Treatment B - Reference Drug: Tagamet® tablet, 1 x 400 mg, SmithKline Beecham, lot #7631T26, expires at 07/31/93, potency 97.5%.

Subjects remained fasted for 4 hours after dosing. Water was not permitted for 2 hours before and 4 hours after dosing except the 240 mL of water taken with each treatment. Blood samples (5 mL each) were collected in vacutainers containing EDTA at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15 and 24 hours postdose.

They were assayed during April 2-24, 1992. The washout period between the administration of two formulations was 14 days.

Analytical Method:

Results:

All 26 subjects completed the study. Fifteen (15) clinical complaints were reported by 6 subjects, 3 during treatment A and 12 during treatment B. The nature of the complaints were runny nose, leg pain, backache, headache, dizziness, vomiting and

lightheadedness. The 12 complaints occurred during treatment B were all considered possibly related to the treatment while the 3 complaints occurred during treatment A were considered not related to the treatment. The reviewer noted that all of the 6 subjects who reported clinical complaints during either treatments had abnormal results in hematology and/or urinalysis during the screening stage.

Samples from the first 12 subjects on each dosing sequence to complete the study were assayed for cimetidine, they were subject #1-22, #24, & #25. Of the 864 samples assayed, 26 were reassayed, 22 due to poor chromatography and 4 due to pharmacokinetic anomaly. The 4 samples repeated due to pharmacokinetic anomaly were each repeated twice and the median values were reported.

The mean plasma concentrations of cimetidine at each sampling point after both treatments in 24 subjects and the mean pharmacokinetic parameters (including $C_{max\ 1st\ peak}$) are presented below in Table 1.

Table 1
Mean (C.V.%) Plasma Cimetidine Concentrations (ng/mL) at Each Sampling Time Point and Means of Pharmacokinetic Parameters (n = 24 -- Fasting Study - 400 mg Tablets)

Time (hour)	Sidmak (Trt. A)	SKB (Trt. B)
0	0	0
0.33	380.4 (122)	337.6 (101)
0.67	1122.6 (53)	1090.7 (54)
1.00	1267.4 (48)	1118.4 (51)
1.33	1316.9 (44)	1177.0 (50)
1.67	1314.3 (43)	1271.0 (37)
2.00	1331.9 (36)	1282.3 (29)
2.50	1292.7 (35)	1342.3 (26)
3.00	1187.6 (35)	1239.0 (25)
4.00	871.9 (32)	951.6 (29)
5.00	584.1 (35)	693.8 (32)

6.00	404.9	(37)	447.9	(28)
8.00	209.7	(41)	231.9	(39)
10.00	91.4	(66)	106.3	(55)
12.00	41.4	(109)	47.8	(84)
15.00	12.1	(201)	7.0	(271)
24.00	2.8	(490)	-	
AUC_{0-t} (ng*hr/mL)	6626.3	(28)	6851.5	(21)
$LNAUC_{0-t}$	8.7610		8.8117	
AUC_{0-inf} (ng*hr/mL)	6909.0	(26)	7058.6	(20)
$LNAUC_{0-inf}$	8.8099		8.8426	
$C_{max\ first\ peak}$ (ng/mL)	1575.8	(46)	1475.5	(38)
$LNC_{max\ first\ peak}$	7.259		7.217	
C_{max} (ng/mL)	1734.5	(38)	1642.4	(29)
LNC_{max}	7.385		7.365	
$T_{max\ first\ peak}$ (hour)	1.091	(43)	0.981	(47)
T_{max} (hour)	1.87	(47)	1.88	(49)
$T_{1/2}$ (hour)	2.51	(94)	1.98	(18)

The %CV of $T_{1/2}$ is much larger for the test product than for the reference product (94% versus 18%). This is due to the different elimination profile between the two treatments for subject #5 whose $t_{1/2}$ was 2.13 hours during period 1 (treatment B) and 13.46 hours during period 2.

Analysis of Variance was performed on each pharmacokinetic parameter, both-untransformed and log transformed, with subject, period, treatment and sequence as factors. No significant period or treatment effect ($p<0.05$) was observed in any of the parameters. There was a slight sequence effect for LNC_{max} ($p=0.0951$). However, this is acceptable since cimetidine is not an endogenous entity; and the study is a single dose study with normal subjects and adequate washout period, which meets all the statistical criteria as shown below in Table 2 (see page 10 of the Guidance of "Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design" issued by the Agency on July 1, 1992).

The LS means of all 4 untransformed and log transformed pharmacokinetic parameters, ratio of these means and the 90% confidence interval of test product versus reference product are presented in Table 2.

Table 2: Statistical Analysis -- Fasting Study

Parameter	LS Means (Sidmak)	LS Means (SKF)	T/R	90% Confidence Interval
AUC_{0-t} (ng*hr/mL)	6626.3	6851.5	0.97	(0.916; 1.019)
$LNAUC_{0-t}$	8.7610	8.8117	0.95	(0.891; 1.013)
AUC_{0-inf} (ng*hr/mL)	6909.0	7058.6	0.98	(0.936; 1.021)
$LNAUC_{0-inf}$	8.8099	8.8426	0.97	(0.924; 1.014)
C_{max} (ng/mL)	1734.5	1642.4	1.06	(0.961; 1.151)
LNC_{max}	7.385	7.365	1.02	(0.924; 1.127)
$C_{max\ first\ peak}$ (ng/mL)	1575.8	1475.5	1.08	(0.944; 1.219)
$LNC_{max\ first\ peak}$	7.259	7.217	1.04	(0.903; 1.205)

Comments:

1. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} as reported by the firm in Table 2 have been confirmed by the reviewer's calculation using the LS means and error mean square presented in the SAS report. They are within the 80-125% range.

2. The data of $C_{max\ to\ first\ peak}$ is for in-house information. It was noted that the double-peak phenomenon was observed in the plasma concentration-time profile for 11 subjects during treatment A and 12 subject during treatment B.

Bioequivalence Study -- Non-Fasting and Fasting:

The objective of this study was to compare (1) the bioavailability of the firm's cimetidine 400 mg tablet and Tagamet® 400 mg tablet manufacture by SmithKline and Beecham,

under non-fasting condition and (2) the bioavailability of the firm's cimetidine 400 mg tablet under non-fasting and fasting condition for labeling purposes.

The clinical portion of the study was conducted at during June 18-19, 22-23, and 26-27, 1992 (group 1) and July 16-18, 20-22 and 24-26, 1992 (group 2) with as the director of the clinical research. The analytical portion was performed in the during June 30-August 3, 1992, with as the analyst.

The design was a single-dose, 3-way crossover in non-fasting and fasting male volunteers. The protocol submitted by the firm was dated June 12, 1992, and amended on July 8 and July 15, 1992. The original protocol with 12 subjects was approved by the Institutional Review Board on was dated June 18, 1992. The reason for the amendments was to add 15 subjects due to the latest FDA guidelines specify a minimum of 24 subjects to be used in the study and additional statistical analysis was required by the Agency. The protocol stated that statistical analyses would be performed on group 1 and the first 4 subjects in each of the 3 sequences in group 2 to complete the crossover study.

A total of 27 male volunteers (2 groups) were enrolled in the study. They were 19-43 years old, weighed within ±15% of the ideal weight for their height and frame size except subject # 16 who was 0.1 Kg overweight. Eleven (11) of them were regular users of tobacco products. The screening procedures included obtaining records of medical history and demographic data and laboratory tests of hemotology, serum chemistry, urinalysis and HIV test. The protocol stated that only medically healthy subjects with clinically normal laboratory profiles would be enrolled in the study. However, 14 of the 27 subjects enrolled had abnormal results of hematology and/or urinalysis. These abnormal results were considered not clinically significant by the investigator.

Exclusion criteria were the same as those stated in the above fasting study.

All 27 volunteers were subjected to the same restrictions and instructions as stated in the fasting study above and received one of the following drug treatments according to a randomly assigned sequence of ABC, BCA or CAB:

Treatment A - Test Drug: Cimetidine tablet, 1 x 400 mg, Sidmak Laboratories Inc., lot #92-008T, potency 98.1% and lot size of [redacted] tablets, given under fasting condition.

Treatment B - Test Drug: Cimetidine tablet, 1 x 400 mg, Sidmak Laboratories Inc., lot #92-008T, potency 98.1% and lot size of [redacted] tablets, given 20 minutes after a standard breakfast*.

Treatment C - Reference Drug: Tagamet® tablet, 1 x 400 mg, SmithKline Beecham, lot #7631T26, expires at 07/31/93, potency 97.5%, given 20 minutes after a standard breakfast*.

* A standard breakfast contained 1 butter English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, hashed browned potatoes, 180 mL of orange juice and 240 mL of whole milk.

Subjects received treatment A remained fasted for 4 hours after dosing. Water was not permitted for 2 hours before and 4 hours after each dosing except the 240 mL of water taken with each treatment. There were 4 days between doses. Blood samples (5 mL each) were collected in vacutainers containing EDTA at 0, 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 15 hours postdose.

They were assayed during June 30-August 3, 1992. The duration of sample storage was [redacted]

Analytical Method:

Results:

Of the 27 volunteers enrolled, subjects #1-12 were enrolled in group 1 and #13-27 in group 2. Prior to period 1 dosing, subjects #14 and #23 were replaced by "standbys" since they did not complete their breakfasts within 20 minutes. Subject # 13 was withdrawn from the study at the time of period 3 check-in because he arrived at the facility in an advanced state of inebriation. Thus a total of 26 subjects completed the study. Plasma samples from all subjects of group 1 and the first 4 subjects in each of the 3 sequences in group 2 to complete the crossover study were analyzed. They were 24 subjects, #1-12, 14-24 and 26.

Ten (10) subjects reported a total of 13 adverse events during this study, 6 during treatment A, 4 during treatment B, and 3 during treatment C. The adverse reactions included headache, feeling depressed, feeling extremely relaxed, constipation, and knee pain. The only symptom considered probably related to the drug treatment was headache. No medication was required for any of these complaints.

Of the 1368 study samples collected, 7 were reassayed due to suspected pharmacokinetic anomaly. Each of these 7 samples was repeated twice and the median value was reported. The mean plasma concentrations of cimetidine at each sampling point after each treatment in 24 subjects and the mean pharmacokinetic parameters are presented below in Table 3.

Table 3

Mean (C.V.%) Plasma Cimetidine Concentrations (ng/mL) at Each Sampling Time Point and Arithmetic Means of Pharmacokinetic Parameters (n = 24* -- Non-Fasting and Fasting Study)

Time (hour)	Sidmak-Fasted (Treatment A)	Sidmak- Fed (Treatment B)	SKB--Fed (Treatment C)
0	0	0[a]	0
0.33	374.8 (105)	44.6 (235)	157.5 (174)
0.67	1150.7 (57)	687.6 (126)	824.9 (94)
1.00	1357.7 (54)	1158.3 (79)	1143.4 (42)
1.33	1405.8 (43)	1304.7 (58)	1245.5 (58)
1.67	1434.2 (31)	1347.5 (36)	1289.5 (45)
2.00	1340.7 (32)	1427.3 (31)	1261.0 (32)
2.50	1271.5 (24)	1271.8 (23)	1220.9 (23)
3.00	1135.5 (23)	1154.8 (25)	1110.0 (30)
3.50	983.8 (23)	960.4 (24)	963.8 (34)
4.00	873.3 (23)	829.6 (25)	807.1 (34)
4.50	774.2 (23)	713.9 (29)	696.8 (40)
5.00	610.6 (21)	568.7 (27)	566.3 (36)
5.50	511.5 (23)	475.6 (27)	475.4 (37)
6.00	397.2 (95)	393.9 (31)	390.7 (38)
8.00	216.2 (32)	211.8 (38)	213.5 (55)
10.00	106.7 (38)	91.5 (58)	90.9 (59)
12.00	43.2 (39)	44.3 (92)	35.3 (120)
15.00	9.8 (229)	0	7.6 (272)
AUC_{0-t} (ng*hr/mL)	6741.8 (22)	6200.3 (22)	6119.5 (20)
$LNAUC_{0-t}$	8.7905	8.7091	8.7015
AUC_{0-inf} (ng*hr/mL)	6937.5 (22)	6437.9 (21)	6325.0 (19)
$LNAUC_{0-inf}$	8.8202	8.7478	8.7353

$C_{max\ first\ peak}$ (ng/mL)	1600.7 (43)	1837.2 (29)	1810.0 (24)
$LNC_{max\ first\ peak}$	7.2885	7.4760	7.4753
C_{max} (ng/mL)	1785.2 (33)	1837.2 (29)	1818.8 (23)
LNC_{max}	7.4357	7.4760	7.4802
$T_{max\ first\ peak}$ (hour)	1.114 (39)	1.828 (46)	1.680 (52)
T_{max} (hour)	1.757 (51)	1.828 (46)	1.722 (53)
$T_{1/2}$ (hour)	2.023 (15)	1.995 (12)	1.982 (15)

* : unless otherwise indicated
a : n = 23

ANOVA was performed on all untransformed and log-transformed pharmacokinetic parameters using a model included group, subject, period, and treatment (3 regimens) as factors, and treatment*group as the interaction term to determine if data from 2 groups could be combined. Subject and period were both nested within group.

There were no significant treatment*group interactions in any of the parameters. In addition, a test of Equality of Variance was performed to determine if there were any significant differences in the variability for the 2 groups for any of the parameters. The test statistic was the ratio of the Mean Square Errors from separate ANOVA for each of the 2 groups of subjects. No significant differences between groups were found for any of the parameters.

The LS means of the pharmacokinetic parameters and their ratios among the 3 treatments are presented in Table 4. The 90% confidence intervals of the four pharmacokinetic parameters, both non-transformed and log-transformed, for treatment B versus treatment are presented in Table 5.

Table 4 - Statistical Analysis-- Non-Fasting and Fasting Study

Treatment	A -Test- Fasted	B- Test - Fed	C-Refer. - Fed		
Parameter	LS Means			Ratio (B/A)	Ratio (B/C)
AUC_{0-t} (ng*hr/mL)	6741.8	6200.3	6119.4	0.92	1.01
$LNAUC_{0-t}$	8.7905	8.7091	8.7015	0.92	1.01
AUC_{0-inf} (ng*hr/mL)	6937.7	6437.9	6325.0	0.93	1.02
$LNAUC_{0-inf}$	8.8202	8.7478	8.7353	0.93	1.01
$C_{max\ first\ peak}$ (ng/mL)	1600.7	1837.2	1810.0	1.15	1.01
$LNC_{max\ first\ peak}$	7.2885	7.4760	7.4735	1.21	1.00
C_{max} (ng/mL)	1785.2	1837.3	1818.8	1.03	1.01
LNC_{max}	7.4357	7.4760	7.4802	1.04	1.00
T_{max}	1.757	1.828	1.722	1.04	1.06

Table 5: 90% Confidence Intervals -- Non-Fasting and Fasting Study

Parameters	90% Confidence Interval of Treatment B/Treatment C
AUC_{0-t}	(0.971; 1.055)
$LNAUC_{0-t}$	(0.970; 1.047)
AUC_{0-inf}	(0.977; 1.059)
$LNAUC_{0-inf}$	(0.975; 1.051)
$C_{max\ first\ peak}$	(0.880; 1.150)
$LNC_{max\ first\ peak}$	(0.866; 1.156)
C_{max}	(0.901; 1.120)
LNC_{max}	(0.894; 1.110)

To determine if a significant carry over effect was present, ANOVA was conducted with an additional term for carryover, i.e., with the 3x3 design of this study, the term for carryover in the model is completely confounded with treatment*period interaction. A significant carryover effect was noted only for the parameter LNC_{max} (p=0.0405). This is however probably due to the difference between the non-fasting and fasting treatments in period 1.

Comments:

1. The ratios of the means of all three pharmacokinetic parameters for the test product versus reference product, both given under non-fasting condition, were all within the 0.8-1.2 limit.

2. The test formulation and the reference formulation were absorbed at almost the same rate (mean C_{max} ratio of 1.01) and to almost the same extent (mean AUC_{0-t} and mean AUC_{0-inf} ratio of 1.01 and 1.02 respectively) under post-prandial condition.

3. When comparing the test product with and without food, the mean AUC and mean C_{max} were almost unchanged and the mean T_{max} was delayed only slightly under non-fasting condition (0.07 hour).

4. The purpose of conducting statistical analysis for this non-fasting study is to provide additional evaluation of bioequivalence in case the 90% confidence intervals from the fasting study did not fall within the required limits. The 90% confidence intervals of all log transformed pharmacokinetic parameters in both fasting and non-fasting studies are within the 80-125% range.

5. The data of $C_{max\ to\ first\ peak}$ is for in-house information. It was noted that the double-peak phenomenon was observed in the plasma concentration-time profile for 10 subjects during treatment A and 1 subject during treatment C.

Dissolution Testing:

The firm has submitted dissolution data on its cimetidine 400 mg Tablet, lot #92-008T, compared to the reference product, Tagamet® 400 mg Tablet, lot #7631T26, manufactured by SmithKline Beecham Pharmaceuticals. The method and results are presented in Table 6.

Table 6. In-Vitro Dissolution Testing- 400 mg Tablet

I. Conditions for Dissolution Testing:

USP XXII Basket xx Paddle ___ RPM 100 No. Units Tested: 12
Medium: Deionized water Volume: 900 ml
Reference Drug: (Manuf.) Tagamet® 400 mg tablet (SKB)
Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min)	Test Product			Reference Product		
	Mean % Dissolved	Range	(%CV)	Mean % Dissolved	Range	(%CV)
	Batch # 92-008T Strength: 400 mg			Lot # 763-1T26 Strength: 400 mg		
5	94.9		(3.3)	84.8		(7.0)
10	98.9		(2.7)	97.2		(1.7)
15	99.8		(2.0)	99.1		(1.5)

Comment:

The dissolution method and results comply with the specification and tolerance of "not less than of cimetidine is dissolved in 15 minutes" as published in the USP 23.

Waiver Request for Cimetidine 200 mg and 300 mg Tablets:

The firm is requesting a waiver of in vivo bioavailability study requirements for the firm's cimetidine 200 mg and 300 mg tablets

based on the results of bioequivalence studies conducted above on the 400 mg product. The comparative formulations of all three strengths of products listed below in Table 7 indicate that all 3 strengths are proportionally identical in its active and inactive ingredients.

Table 7: Comparative Formulations of 200 mg, 300 mg and 400 mg Cimetidine Tablets Manufactured by Sidmak Laboratories

ingredient	400 mg	300 mg (mg/tablet)	200 mg
Core			
Cimetidine, fine powder	400.0	300.0	200.0
Microcrystalline Cellulose			
Sodium Starch Glycolate			
Pregelatinized Starch			
Sodium Lauryl Sulfate			
Providone			
Magnesium Stearate			
Colloidal Silicon Dioxide			
Total Weight of the Core	560.00	420.00	280.00
Coating and Printing			
Yellow			
Clear			
Carnauba Wax Powder			
Vanilla Artificial Flavor			
Black Ink			
Total weight of Tablet	578.4	433.289	289.2

The firm has submitted dissolution data on its Cimetidine 200 mg and 300 mg Tablets, lot #92-016T and #92-017T respectively, compared to the reference product, Tagamet® 200 mg tablet and 300 mg tablet respectively. The method and results are presented in

Table 8.

Table 8. In-Vitro Dissolution Testing- 200 mg Tablets

I. Conditions for Dissolution Testing:

USP XXII Basket xx Paddle ___ RPM 100 No. Units Tested: 12
Medium: Deionized water Volume: 900 ml
Reference Drug: (Manuf.) Tagamet® 200 mg Tablet (SKB)
Assay Methodology: _____

II. Results of In-Vitro Dissolution Testing:

Sampling Times (min)	Test Product		Reference Product	
	Mean % Dissolved	Range (%CV)	Mean % Dissolved	Range (%CV)
	Batch # 92-016T Strength: 200 mg		Lot # 5011T12 Strength: 200 mg	
5	98.4	(1.3)	93.1	(1.5)
10	99.9	(1.0)	97.8	(1.8)
15	100.4	(0.8)	99.7	(1.6)
	Batch # 92-017T Strength: 300 mg		Lot # 511T13 Strength: 300 mg	
5	98.5	(1.7)	88.9	(7.6)
10	99.1	(1.0)	98.0	(1.9)
15	100.1	(1.0)	98.6	(1.6)

Comments:

The dissolution method and results comply with the specification and tolerance of "not less than of cimetidine is dissolved in 15 minutes" as published in the USP 23.

Recommendation:

1. Both bioequivalence studies, fasting and non-fasting, conducted by Sidmak Laboratories, Inc. on its cimetidine tablet, 400 mg, Lot #92-008T, comparing to Tagamet® 400 mg tablet, manufactured by SmithKline Beecham, have been found acceptable by the Division of Bioequivalence. The studies demonstrated that Sidmak's cimetidine tablet, 400 mg, is bioequivalent to the reference product, Tagamet® 400 mg Tablet manufactured by SmithKline Beecham when administered under either fasting or non-fasting condition.

2. The dissolution testing conducted by Sidmak Laboratories, Inc. on its three strengths of cimetidine tablets, 200 mg, 300 mg and 400 mg, Lot #92-016T, #92-017T, and #92-008T respectively, are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of deionized water at 37° using USP 23 apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of cimetidine in the dosage form is dissolved in 15 minutes.

3. The waiver of in vivo bioequivalence study requirements for the firm's cimetidine tablets, 200 mg and 300 mg, are granted per 21 CFR320.22(d)(2). The 200 mg and 300 mg tablets of the test product are therefore deemed bioequivalent to Tagamet®, 200 mg and 300 mg respectively, manufactured by SmithKline Beecham.

Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 6/12/95

Concur: _____ Date: 6/15/95
Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA 74-568 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (Cviswanathan), HFD-652 (Huang, Chuang), Drug File, Division File

LWC/060795/dbm/WP74-568